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Combination of gemcitabine and cisplatin for biliary tract cancer: A platform to build on

Nataliya Razumilava*, Gregory J. Gores

Division of Gastroenterology and Hepatology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

COMMENTARY ON:

Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. N Engl J Med 2010 Apr 8;362(14):1273–81. Copyright (2010) Massachussets Medical society. All rights reserved. Abstract reprinted with permission from the Massachussets Medical society.

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Background: *There is no established standard chemotherapy for patients with locally advanced or metastatic biliary tract cancer. We initially conducted a randomized, phase 2 study involving 86 patients to compare cisplatin plus gemcitabine with gemcitabine alone. After we found an improvement in progression-free survival, the trial was extended to the phase 3 trial reported here.*

Methods: *We randomly assigned 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive either cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter on days 1 and 8, every 3 weeks for eight cycles) or gemcitabine alone (1000 mg per square meter on days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks. The primary end point was overall survival.*

Results: *After a median follow-up of 8.2 months and 327 deaths, the median overall survival was 11.7 months among the 204 patients in the cisplatin–gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval, 0.52–0.80; p <0.001). The median progression-free survival was 8.0 months in the cisplatin–gemcitabine group and 5.0 months in the gemcitabine-only group (p <0.001). In addition, the rate of tumor control among patients in the cisplatin–gemcitabine group was significantly increased (81.4% vs. 71.8%, p = 0.049). Adverse events were similar in the two groups, with the exception of more neutropenia in the cisplatin–gemcitabine group; the number of neutropenia-associated infections was similar in the two groups.*

Conclusions: *As compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity. Cisplatin plus gemcitabine is an appropriate option for the treatment of patients with advanced biliary cancer. (ClinicalTrials.gov number, NCT00262769.)*

Biliary tract cancers (BTC) are a heterogeneous group of carcinomas with features of cholangiocyte differentiation originating from the epithelium of the bile ducts and gallbladder. They can be classified into cholangiocarcinoma (CCA; intrahepatic, perihilar, and extrahepatic), gallbladder carcinoma (GBC), and ampullary cancer. Each of these is characterized by distinct clinical behaviors and genetic signatures. These tumors are highly lethal due to the advanced stage at diagnosis, poor response to systemic therapy, and a high rate of recurrence after surgical treatment. Additionally, there is a trend toward increasing incidence of BTC, mainly due to an increase of intrahepatic CCA. Over the last 25 years, the five-year survival rate remains dismal (<10%) [1]. Because of disease heterogeneity, associated cholestatic liver dysfunction and small numbers, BTC have been seldom studied in clinical trials employing systemic therapy.

Studies evaluating the efficacy of cytotoxic chemotherapeutic agents for BTC have examined fluorouracil, gemcitabine, cisplatin, oxaliplatin, and mitomycin C. These studies suggested that the combination of gemcitabine plus platinum-based agents is the palliative option with the greatest potential [2]. However, these studies were underpowered phase 2 trials with limited evidence favoring one combination over another. Reports on the tolerability of gemcitabine-based regimens versus solo treatment with gemcitabine described more side effects with the dual therapy, with up to >50% study withdrawal rate [3]. Establishment of a baseline chemotherapeutic regimen based on well-powered, randomized-controlled trials was a long-awaited step for BTC. Toward this goal, Valle and colleagues conducted a multicenter phase 3 randomized-controlled trial to define the efficacy and tolerability of gemcitabine alone versus its combination with cisplatin for the treatment of locally advanced and metastatic BTC (the Advanced Biliary Cancer [ABC]-02) [4]. This trial was a successful extension of a positive phase 2 trial (the ABC-01) which used the same eligibility criteria and randomization [5]. The timely transition and identical design of the ABC-01 and ABC-02 allowed incorporating the data from phase 2 into a phase

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* Corresponding author. Address: Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA. Tel.: +1 507 284 0686; fax: +1 507 284 0762.

E-mail address: gores.gregory@mayo.edu (N. Razumilava).

3 trial, which represents a unique study design. The primary outcome was overall survival (OS); the secondary outcomes were progression-free survival (PFS), tumor response, and adverse effects. Patients with serum liver enzymes $\geqslant$5 times the upper limit of normal, and/or a serum total bilirubin $\geqslant$1.5 times the upper limit of normal were excluded from the study.

The study of Valle *et al.* demonstrated an improvement in OS in the gemcitabine–cisplatin group as compared to gemcitabine alone (11.7 months versus 8.1 months, p <0.001). PFS was also improved in the combination group as compared with the gemcitabine-only group (8.0 months versus 5.0 months, p <0.001). The overall risk of dying was 36% less in the gemcitabine–cisplatin group (hazard ratio 0.64; 95% CI, 0.52–0.80). However, when the patients' subgroups were examined, significant response rates were achieved primarily in patients with GBC and intrahepatic CCA. The confidence intervals for the hazard ratio for both perihilar and ampullary BTC subgroups crossed one and did not achieve statistical significance. This may be due to a lack of statistical power for the individual subgroups (only 20 patients with ampullary carcinoma and 57 with peripheral disease) or due to the different biology of these cancers.

The tolerability profile was reported to be similar between treatment arms, except for the frequency of neutropenia, which did not translate into an increased rate of neutropenia related infections. However, keeping in mind that palliative care is focused on alleviating the severity of symptoms, improving the quality of life and psychosocial wellbeing, we need to be more critical and attentive to side-effects influencing these parameters. The ABC-01 trial demonstrated a striking prevalence of lethargy in the combination arm versus gemcitabine alone (28.6% vs 9.1%). Stomatitis, diarrhea, and pain, potentially influencing quality of life, also were more prevalent in the combination arm in the ABC-01. Unfortunately, none of these adverse effects was commented on the ABC-02 trial. A cost-effectiveness analysis is another essential component in the decision-making process. Apparently these analyses may be presented in forthcoming publications, and we await this information.

What can we advise our patients based on the Valle *et al.* study? Gemcitabine–cisplatin combination modestly improves survival in GBC and intrahepatic CCA, though it is not curative, and there are no data available measuring the quality of life. Clearly, the survival advantage of the combination is modest, and continued studies are necessary to eventually cure this disease. Where do we go from here, especially with less toxic targeted therapies? Most of our patients have perihilar disease with serum bilirubin $\geqslant$1.5 times the upper limit of normal, despite endoscopic placement of biliary stents. We would argue that for these patients equipoise still exists and trials of a targeted agent versus gemcitabine plus cisplatin would be most informative. Promising targeted therapies include the epidermal growth factor receptor (EGFR) inhibitor cetuximab and mitogen-activated protein kinase (MEK) inhibitors, for which there are several in development [6]. For GBC or intrahepatic CCA, gemcitabine–cisplatin combination will be the standard of care for eligible patients (nonicteric, performance status $\leqslant$2). Targeted therapies can be added to this regiment or studied as a second line therapy. Phase 3 trials should be based on rigorously designed phase 2 trials utilizing comparator arms [7]. The ABC-2 success will hopefully encourage further interest in beating this devastating disease. We still have a long way to go.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript

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